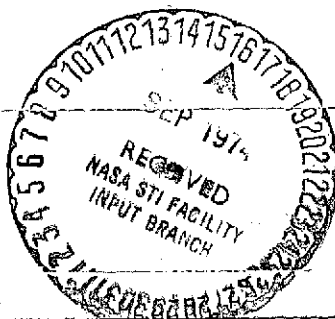


LUPUS INDUCED BY D-PENICILLAMINE DURING TREATMENT OF
RHEUMATOID-ARTHRITIS 20 CASES AND IMMUNOLOGICAL STUDY
DURING TREATMENT

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Translation of: "Lupus induit par la D-Penicillamine
au cours du traitement de la polyarthrite rhumatoïde."
In: Annales de Medecine Interne, v. 125, no. 1, pp. 71-79,
1974.



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| (NASA-TT-F-15738) LUPUS INDUCED BY | N74-31566 |
| D-PENICILLAMINE DURING TREATMENT OF | |
| RHEUMATOID-ARTHRITIS: TWO CASES AND | |
| (Linguistic Systems, Inc., Cambridge, | Unclas |
| Mass.) 24 p HC \$4.25 | CSCL 06E G3/04 47769 |

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|--|--|--|-----------|
| 1. Report No. NASA TT F- 15738 | 2. Government Accession No. | 3. Recipient's Catalog No. | |
| 4. Title and Subtitle LUPUS INDUCED BY D-PENICILLAMINE DURING TREATMENT OF RHEUMATOID-ARTHRITIS 2 CASES AND IMMUNOLOGICAL STUDY DURING TREATMENT. | | 5. Report Date August 1974 | |
| 7. Author(s) Crouzet, J. et al. | | 6. Performing Organization Code | |
| 9. Performing Organization Name and Address LINGUISTIC SYSTEMS, INC. 116 AUSTIN STREET CAMBRIDGE, MASSACHUSETTS 02139 | | 8. Performing Organization Report No. | |
| 12. Sponsoring Agency Name and Address NATIONAL AERONAUTICS AND SPACE ADMINISTRATION WASHINGTON, D.C. 20546 | | 10. Work Unit No. | |
| | | 11. Contract or Grant No. NASW-2482 | |
| | | 13. Type of Report & Period Covered TRANSLATION | |
| | | 14. Sponsoring Agency Code | |
| 15. Supplementary Notes Translation of: "Lupus induit par la D-Penicillamine au cours du traitement de la polyarthrite rhumatoide." In: Annales de Medecine Interne, v. 125, no. 1, pp. 71-79, 1974. | | | |
| 16. Abstract In investigations of Lupus induced by D-Penicillamine during treatment for rheumatoid arthritis, the course of two cases is described in detail. Then, results of a study of 25 arthritics for biological signs of Lupus during D-Penicillamine treatment of rheumatoid arthritics are examined. The cases and systematic survey confirm findings in the literature and allows definition of general clinical and biological aspects of this syndrome which appear after 10 months of treatment. | | | |
| 17. Key Words (Selected by Author(s)) | | 18. Distribution Statement UNCLASSIFIED - UNLIMITED | |
| 19. Security Classif. (of this report) UNCLASSIFIED | 20. Security Classif. (of this page) UNCLASSIFIED | 21. No. of Pages | 22. Price |

LUPUS INDUCED BY D-PENICILLAMINE DURING
TREATMENT OF RHEUMATOID ARTHRITIS

TWO CASES AND A SYSTEMATIC IMMUNOLOGIC STUDY
OF THE COURSE OF TREATMENT

J. Crouzet*, J.-P. Camus, A.-P. Leca, P. Guillen,
and J.-A. Lièvre

It is now three years since M. Boudin and M. Caille presented 171* herein the first cases of lupus erythematosus induced by D-penicillamine. Since then, several others have been noted. All these cases involve the treatment of Wilson's disease or cystinuria.

We report here two cases of lupus induced by D-penicillamine in the course of treatment of rheumatoid arthritis. We present as well the results of a systematic study of the biology of lupus before and during such treatment.

I. Observations

Case 1. Mrs. Solange Bri..., 45 years old, with no previous personal or familial pathological history.

Her arthritis begins in 1966 as inflammatory-like pain in the right shoulder and recurs in 1967 in the form of arthritis of the metacarpophalanges and proximal interphalanges of both hands, and then in the knees.

*Fellow of the study Fund of the Medical Hospital Corp. Communication presented to the Medical Society of Paris Hospitals. November 16, 1973 conference.

**Numbers in the margin indicate pagination in the foreign text.

A treatment consisting of aspirin, chloroquine, and corticoids brings about transitory improvement and a Cushing-like syndrome.

At the end of 1968 there occurs a major advance in the progress of the disease: knees, shoulders, elbows, wrists, and hands are affected. A visceral examination is completely negative. Biological tests reveal a sedimentation rate of 42 mm in the first hour, a Waaler-Rose reaction, and a negative Latex test. No LE cells can be found.

The progress of the disease is slowed by increasing the dosage of corticoids, and the disease stays quiescent using aspirin, non-cortisone anti-inflammatory agents, and injection of corticoids into the knee.

In February 1971, new extensive progress of the disease affecting the temporomaxillaries and the hips. Cutaneous and visceral tests negative. Biological tests: sedimentation rate 12 mm during the first hour; red cells: 4,900,000; white cells: 7,100; polynucleated neutrophiles: 65%; eosinophiles: 5%--negative Waaler-Rose and Latex reactions. Treatment with D-penicillamine is started on 27 March 1971, 750 mg per day for three weeks, then 1 g per day.

Biological testing on 19 April 1971: sedimentation rate 15 mm during the first hour; red cells: 4,300,000; white cells: 8,100; polynucleated neutrophiles: 75%; eosinophiles: 1%. Waaler-Rose and Latex tests negative, antinuclear antibodies have homogeneous fluorescence at 1/50 (immunofluorescence method using liver sections).

In July 1971, all articulation pains are gone, the visceral examination is negative. Nonetheless the patient shows a prurigenous sun erythema already observed earlier in 1970 and 1969. Histologic tests: sedimentation rate 8 mm during the first hour; hemogram: normal; antinuclear antibodies: 1/100 (same method). Only D-penicillamine is continued at a dosage of 1 g per day followed by 1.5 g per day because of a momentary attack in September 1971.

In February 1972, painful acute attack of a different character than the preceding ones: the pains are diffuse, essentially muscular, affecting the arms, the forearms, the thighs, and the waist. An increase in D-penicillamine dosage to 2 g per day further aggravates the myalgias which become permanent (March 1972).

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Clinical examination shows no visceral or cutaneous lesion. Biological examination: sedimentation rate: 11 mm during the first hour; normal hemogram. Protein electrophoresis: 10% α -1 globulins, 10% α -2, 24% gammaglobulins; urea: 0.24 g/liter; negative Waaler-Rose and Latex. Numerous LE cells on three successive examinations. Antinuclear antibodies positive at 1/500 (same method) with a homogeneous image.

The diagnosis of lupus induced by D-penicillamine is then made and treatment interrupted on March 23.

The outcome is spectacular: the muscular pains disappear completely in 10 days. Articulation pains are moderate. They vanish with 100 mg of indocid and 1 g of aspirin per day.

In June 1972, with this treatment the clinical state is satisfactory. No visceral signs. Biology: sedimentation rate 10 mm during the first hour, normal hemogram, numerous LE cells, antinuclear antibodies: 1/1,100 homogeneous.

In September 1972: identical results.

In March 1973: satisfactory clinical state with the possibilities for normal work. Biology: Waaler-Rose and Latex negative. No LE cells, antinuclear antibodies positive at 1/500.

Summary: Typical although sero-negative rheumatoid arthritis, with no visceral anomalies, treated successfully with D-penicillamine. In the eleventh month, development of muscular hyperalgy with appearance of very positive lupus serology. Rapid disappearance of clinical signs upon stopping treatment, but persistence of biological abnormalities one year later.

Case 2. Mrs. Jeanne Gen..., 53 years old, with no personal or familial pathological history.

Arthritis begins in June 1969 with pains in the shoulders, the wrists, and the knees. In October 1969, sedimentation rate: 20 mm during the first hour; Waaler-Rose reactions: 1/128; no LE cells. Treatment with chloroquine and ACTH is started.

In October 1970, the patient consults one of us, who notes arthritis of the shoulders, elbows, wrists, metacarpophalanges, and cervical spine. Clinical examination: no visceral lesions. No rheumatoid nodules. Ocular examination: a few corneal deposits which force the discontinuation of chloroquine treatment.

In January 1971, significant worsening of articulation. Biological examination: sedimentation rate: 25 mm during the first hour; normal hemogram; Waaler-Rose: positive 1/1,024, no LE cells; antinuclear antibodies negative (immunofluorescence using liver sections); absence of anti-DNP (Latex) antibodies.

Treatment with D-penicillamine is begun February 10, 1971 at a dosage increasing to 1.25 g per day on May 26, with 5 mg of prednisone.

In November 1971, the articular pain disappeared except for some arthralgia in the fingers.

In January 1972, 11 months after the beginning of this treatment, a new appearance of the symptoms: redness and pruritis of the eyelids and the cheeks, with light edema, pain in the hands, shoulders, ankles, and knees. Biology: sedimentation rate: 17 mm during the first hour; normal hemogram. No proteinuria, absence of LE cells, antinuclear antibodies (immunofluorescence using liver sections): positive reaction at 1/500 (homogeneous appearance), absence of anti-DNP antibodies, negative Waaler-Rose.

Treatment with D-penicillamine is continued at a dose of 1 g per day, corticotherapy is stopped.

In April 1972, facial rash has disappeared but articulation pains increase and necessitate resumption of corticotherapy (5 mg of prednisone). Treatment with D-penicillamine is stopped because of leucopenia (3,500) and thrombopenia (88,000). The hemogram returns to normal in 15 days.

In December 1972, six months after the discontinuation of D-penicillamine and despite corticotherapy, there is significant polyarticular relapse without visceral signs.

Biology: sedimentation rate: 43 mm during the first hour; hemogram: normal; Waaler-Rose: 1/256; no LE cells; no anti-DNP antibodies.

We decided to resume treatment with D-penicillamine. Two months later (February 1973) clinical improvement is evident. There is no sign of lupus. Blood analysis is normal, except for the presence of Heller B cells and a positive reaction at 1/100 in the test for antinuclear antibodies by immunofluorescence.

In July 1973, the subjective state is good, the general examination is negative. Biological evaluation shows a sedimentation rate of 7 mm during the first hour, a normal hemogram, a Waaler-Rose reaction at 1/128, antinuclear antibodies still positive at 1/50 by immunofluorescence. /73

In September, immunofluorescence of a homogeneous type is positive at 1/1,000. Anti-DNP antibodies are absent. In October, non-infiltrated erythematous spots appear, with a thinning of the epidermis on the anterior surface of the thorax (Dr. Noble). Globular sedimentation at this point is 15 mm during the first hour and the white cell count at 4,500. Biopsy of a cutaneous specimen shows some elements favoring a "lupiform eruption," and others favoring a toxidermia (Dr. Lessana-Leibowitch).

Summary: Typical seropositive rheumatoid arthritis, without visceral abnormality, treated with D-penicillamine with good clinical and biological results for ten months. In the 11th month, appearance of an eruption on the face and a large increase in antinuclear antibodies; the eruption disappears despite the continuation of treatment. The subsequent discontinuation of D-penicillamine is followed by articulative relapse; renewal of the treatment occurs without incident at the outset and antinuclear antibodies continue to diminish. In the tenth month, an eruption compatible with the diagnosis of lupus reappears, preceded by an increase in the antinuclear antibody titers.

II. Development of the Biological Evidence of Lupus during Treatment of Rheumatoid Arthritis with D-penicillamine

The appearance of lupus in the course of Wilson's disease and cystinurias treated with D-penicillamine, and the absence of known connections between these two diseases and lupus erythematosus strongly suggest that D-penicillamine, like many other drugs, is capable of inducing "iatrogenic" lupus.

In rheumatoid arthritis, whose features common with lupus are even more uncertain, one may ask whether D-penicillamine reveals a latent lupus appearing in the form of an arthritis, or whether it is a matter of a purely iatrogenic lupus as indicated by Case 1 where the clinical muscle syndrome ceased immediately on stoppage of treatment.

In order to obtain some partial answers to this question we studied in 25 arthritics the evolution of certain biological signs of lupus before and during treatment with D-penicillamine.

1) Material: Our 25 arthritics consist of 23 women and 2 men. There are 19 cases of "classical" arthritis and 6 cases of "typical" arthritis (using A.R.A. criteria).

Rheumatoid serology is positive in 20 cases.

The average age is 51 years, the extremes being 39 and 71 years.

In no case do any visceral or cutaneous signs accompany the articulative manifestations prior to treatment. None of these 25 patients, with the exception of the two cases reported here, had clinical signs during treatment that could make one fear an induced lupus.

Treatments with D-penicillamine were administered at doses of 12 to 30 mg/kg/day, and the average duration of treatment was 14 months (extremes 3 and 36 months).

2) Methods: we studied the following tests before and during treatment:

a) Hargraves cells by the clotting method (Zimmer and Hargraves [1958]);

b) Antinuclear antibodies by indirect immunofluorescence using liver sections (IF) following the method of Hamard and Seligman [1964];

c) Anti-DNP antibodies (Latex test according to Christian [1958]);

d) Lymphoblastic transformation test (LTT) in the presence of calf thymus DNA following a method derived from that of Halpern (1967) carried out in only 12 cases.

3) Results

-- Hargraves cells (Table I). These were looked for in 24 cases (the survey was not performed initially in Case 1). Before treatment the search is negative in 22 cases, and twice Heller B cells are found but never any Hargraves cells.

During treatment 19 tests are negative, B cells are found 5 times, never LE cells.

TABLE I. L.E. CELLS FOUND BEFORE AND DURING TREATMENT

| | Negative | B. Cells | L.E. Cells |
|------------------|----------|----------|------------|
| Before Treatment | 22 | 2 | 0 |
| After Treatment | 19 | 5 | 0 |

-- Antinuclear antibodies (IF) (Table II). Prior to treatment the results were negative 15 times, positive 9 times with a titer less than or equal to 1/100, equal to 1/500 one time.

During treatment, among the 15 negatives at the outset, it became positive often at low titers, but two reached 1/500.

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Among the 10 positives at the outset, 5 decrease and 3 become negative and 5 increase, 3 of them by at least two dilutions.

Table II records the result of the last immunofluorescence carried out for each patient, which for some of them does not correspond to the highest antibody titer observed in successive assays.

-- Anti-DNP antibodies. Studied in every case, they remained negative during treatment, except for the 2 cases where clinical signs of lupus appeared.

-- Lymphoblastic transformation test in the presence of DNA (Table III). This test was performed on 12 patients, before and after an average treatment of 22 months.

TABLE II. ANTINUCLEAR ANTIBODIES SEEN IN IMMUNOFLUORESCENCE

| H = Homogeneous Type Fluorescence M = Mottled Type Fluorescence | | | | |
|--|---|-----------------|---------------|----------------------------|
| Number | Duration of treat- ment (months) | Dose Mg/kg/J | FAN before | FAN during treatment |
| 1 | 14 | 16 then 12 | 0 | 0 |
| 2 | 29 | 20 then 41 | 0 | 0 |
| 3 | 3 | 16 | 0 | 0 |
| 4 | 3 | 18 | 0 | 0 |
| 5 | 3 | 17 | 0 | 0 |
| 6 | 4 | 17 | 0 | 1/10 |
| 7 | 3 | 28 | 0 | 1/10 |
| 8 | 8 | 20 then 15 | 0 | 1/50 H |
| 9 | 10 | 14 | 0 | 1/50 H |
| 10 | 6 | 12 | 0 | 1/50 M |
| 11 | 24 | 16 | 0 | 1/50 H |
| 12 | 6 | 23 then 14 | 0 | 1/50 H |
| 13 | 28 | 34 | 0 | 1/100 H |
| 14** | 11 | 25 | 0 | 1/500 H |
| 15 | 36 | 30 | 0 | 1/500 H |
| 16 | 28 | 19 | ± 1/1 | 1/100 H |
| 17 | 28 | 14 then 5 | 1/1 | 0 |
| 18 | 9 | 16 | 1/10 | 0 |
| 19 | 6 | 13 | 1/10 | 1/50 M |
| 20 | 15 | 13 | 1/10 | 1/100 H |
| 21* | 10 | 17 then 20 | 1/50 H | 1/500 H |
| 22 | 6 | 14 then 21 | 1/100 H | 1/50 |
| 23 | 26 | 23 | 1/100 M | 0 |
| 24 | 29 | 16 | 1/100 M | 1/1 |
| 25 | 4 | 15 then 17 | 1/500 H | 1/1 000 M |

*Case no. 1
**Case no. 2

-- Before treatment: the test is negative in all cases.

-- During treatment: eleven patients remain negative, only one becomes positive without altering his titer of antinuclear antibodies.

In summary: The LE cell survey very often gives negative results with respect to immunofluorescence. We have found evidence of LE cells only in Case 1 at the peak of the lupus attack.

Immunofluorescence gives positive results in approximately one-half the cases. Thirteen times out of twenty-five (52%) antibodies appear or increase in titer to a significant extent. The presence in this series of 25 cases of 2 clinical cases motivating systematic study is consistent with the frequency of immunologic abnormalities.

Anti-DNP antibodies remain absent.

The lymphoblastic transformation test remains negative during treatment. It is, as we have noted (Crouzet [1971]), usually negative in arthritis, in contrast to what is observed in autonomous lupus (Patrucco [1967], Reinert [1971]).

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The essential immunologic manifestation is thus the appearance of antibodies detectable by immunofluorescence.

Moreover, the daily dose of D-penicillamine does not appear to play a clear role, since it is 18 mg/kg in the "negatives" and 20 in the "positives."

The decrease in dosage of cortisone which is made possible by penicillamine is likewise not a factor, since patients who remain free of antibodies are more often deprived of corticoids than the others.

Antibodies appear or increase after very variable periods of treatment, sometimes as soon as the 3rd month. Conversely, prolonged treatments can be without any effect.

The increase in titer of antibodies present initially is not any more frequent than the appearance of antibodies where they were absent.

TABLE III. L.T.T. IN THE PRESENCE OF DNA. 12 PATIENTS. AVERAGE LENGTH OF TREATMENT (22 MONTHS)

| Number | L.T.T. | F.A.N. at the time of L.T.T. |
|--------|----------|---------------------------------|
| 1 to 4 | negative | 0 |
| 5 | negative | 1/10 |
| 6 | negative | 1/100 H |
| 7 | negative | 1/100 H |
| 8 | negative | 1/100 M |
| 9 | negative | 1/500 H |
| 10 | positive | 1/100 M |
| 11 | negative | not tried |
| 12 | negative | not tried |

III. Discussion

The two cases reported in the first part of this paper and the systematic study of the biology of lupus during arthritis treated with D-penicillamine confirm the findings in the literature (Boudin, Caille, Olivier, Rasmussen, Walshe) (Tables IV and V).

1) They allow one to define the general clinical and biological aspects of this syndrome which seem to appear after a minimum of 10 months of treatment.

The clinical signs are dominated by cutaneous signs, arthralgia and myalgia. In no case is any definite evidence of renal involvement noted. All in all, they conform to the description of iatrogenic lupus (Dorfman [1973]).

From the biological point of view, the increase in sedimentation rate is frequent but not constant. The leucopenias and thrombopenias are attributable either to the lupus or to the hematologic effect of D-penicillamine, or else to Wilson's disease.

The clearest immunological effects concern the antinuclear antibodies detected by the indirect immunofluorescence method. The numbers which we obtain in our systematic study make it appear that 52% of the arthritis cases treated with D-penicillamine produce antibodies. These numbers are reminiscent of those obtained by other authors with other drugs: with procainamide, one observes the appearance of antibodies 65% of the time (Dubois [1965]), with hydralazine 50% (Condemi [1967]), with isoniazide 20% (Cannat [1970]).

Our results indicate a similarity between D-penicillamine, procainamide, and hydralazine with respect to the incidence of antinuclear antibodies. Nonetheless, it is important to note that diseases treated with these two drugs do not have any relation to spontaneous lupus erythematosus as arthritis does, and are unconnected to any immunologic abnormalities.

The negativity of LTT with respect to the native DNA of our patients treated and developing fluorescent antibodies

corroborates the classical notions concerning the absence of anti-native DNA antibodies in induced lupus, in contrast to what we usually find in spontaneous lupus. The recent work of Hahn [1971] and Kahn [1973] have made it possible, however, to demonstrate anti-native DNA antibodies in induced lupus. Hahn [1972] reports in addition one case of positive LTT.

TABLE IV. CLINICAL TABLE OF 6 OBSERVED CASES OF LUPUS INDUCED BY D-PENICILLAMINE

| Authors | Boudin | Caille | Ramussen | Oliver | Personal Observation | |
|-----------------------|-----------|----------|------------|------------|----------------------|-----------|
| | | | | | N° 1 | N° 2 |
| Disease treated | Wilson's | Wilson's | Cystinurie | Cystinurie | FR | FR |
| Dose | 1g/day | 3g/day | 1g/day | 1.8g/day | 1.50g/day | 1.25g/day |
| Length of treatment | 2 years | 1 year | 1 year | 19 months | 11 months | 10 months |
| Age | 21 years | 22 years | 22 years | 47 years | 44 years | 52 years |
| Sex | F | F | M | F | F | F |
| Arthralgias | + | + | + | + | + | + |
| Renal involvement | 0 histo — | 0 | 0? | 0 | 0 | 0 |
| Myalgias | | + | | | ++ | 0 |
| Cutaneous involvement | + histo + | + | + | | | + |
| Heart | | + | | 0 | | |
| Lungs | | | | 0 | | |
| Pleura | | + | | 0 | | |
| Abdominal pains | | + | | | | |
| Fever | 38,5 | 38 | | none | none | none |

2) The frequency of lupus induced by penicillamine is still difficult to measure. During Wilson's disease and cystinuria, 4 cases have been published in detail and others have been mentioned: two by Walsche [1968] for several tens of treated patients, one by Mirouze [1973]. Boudin [1973] observes altogether two cases out of 21 patients with Wilson's disease treated with penicillamine.

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TABLE V. BIOLOGICAL TABLE OF 6 OBSERVED CASES OF LUPUS INDUCED BY D-PENICILLAMINE

| Authors | Boudin | Caille | Ramussen | Oliver | Personal observations | |
|------------------|----------|--------|----------|--------|-----------------------|-------|
| | | | | | N°1 | N°2 |
| V.S. | 50 | 60 | | 45 | 11 | 17 |
| L.E. | + | 0 | + | + | + | + |
| AC. AN. X.F. | 1/10 000 | 1/500 | | 1/960 | 1/500 | 1/500 |
| AC. AN. (DNP) | | + | + | | — | — |
| G.R. | | | | | 4,3 M | 4,8 N |
| G.B. | | 1 200 | | | 6 300 | 4 000 |
| W.R. | — | — | | | — | — |

In rheumatoid arthritis our series of 100 cases (Camus [1973]) includes the two cases which we report here. In the other series in the literature which comprise a total of more than 800 arthritics receiving penicillamine (Payne [1969], Tanner [1969], Jaffe [1970], Zuckner [1970], Golding [1970], Miehle [1971], Maldikowa [1972], Truhlar [1972], Lancet [1973], Krüger [1973], Chlud [1973], Mathies [1973]) this complication is not mentioned.

With respect to latent biological abnormalities, let us note that Scheinberg [1968] found evidence of antinuclear factor (anti-DNP?) one time out of 24 in patients treated for Wilson's disease or cystinuria.

It does not appear, therefore, that lupus induced by penicillamine should be any more common in arthritis than in other diseases without immunologic abnormalities. However, Alarcon-

Segovia [1969] thinks that the pathogenesis of induced lupus involves the intervention, apart from drug-related factors, of a genetic predisposition and of immune disorders, from which arthritis is not excluded if the criterion is the frequency of anti-nuclear antibodies in the disease even before any treatment which is reputed to be inductive.

3) The pathogenesis of lupus induced by D-penicillamine is uncertain. Penicillamine denatures certain proteins by reacting with disulfide bridges, or modifies their synthesis (Blumentrantz [1973]). This is reminiscent of the denaturing effect of hydralazine and of INH (Tan [1968], Alarcon-Segovia [1971]). Penicillamine could act in this way.

Penicillamine is an antigen or a hapten, as shown by the work of Amos [1968] and of Harpey [1971]. It is known that antibodies can be discovered against the most strongly inducing drugs, hydralazine (Heine [1962]) and procainamide (Russel [1968]).

Finally, lupus induced by penicillin (Gold [1951]) could sometimes be linked to the presence of penicillamine at the end of the chain by reason of the existence of cross-allergic phenomena (Caron [1973], Camus [1973]).

4) The evolution of the lupus induced by D-penicillamine has been favorable in all the cases described. In contrast, the immunologic effects can persist for several months.

The existence of purely biological manifestations of anti-nuclear immunity does not seem to us to be an a priori contraindication for penicillamine, especially since it is used also in the treatment of active chronic hepatitis (Lange [1971]). It certainly does call for more careful surveillance in all areas.

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